REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claims 1, 3, 5-7 and 9-11 are pending in this application.

Claims 6, 7 and 9 are indicated as withdrawn on the Office Action Summary page. However, during a telephonic interview with the Examiner, she indicated that claims 6, 7 and 9 were rejoined, and thus are not withdrawn from consideration.

Claim 1 has been amended to change "consisting essentially of" to "comprising", and to further narrow the organic amine to be selected from the group consisting of "arginine, histidine, aspartic acid, glutamic acid, serine, threonine, cysteine, phenylalanine, isoleucine, monoethanolamine, diethanolamine, triethanolamine, trometamol, 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid, 1,4-bis(2-sulfoethyl)-piperazine, ethylene diamine, trimethylene diamine, N,N'-bis(3- sulfopropyl)ethylene diamine, aminomethylsulfonic acid and aminoethylsulfonic acid". Support for this amendment can be found on page 13, lines 19-29 of the specification.

Claims 5-7 and 9-11, have been amended to further define the organic amine.

I. Claim Rejection Under 35 U.S.C. § 112

The Examiner rejects claims 1, 3 and 5 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner asserts that claims 1 and 5 recite the broad recitation "amino acid", and that "aminoalkylsulfonic acid" is narrower than amino acid. The Examiner further indicates that aminoalkylsulfonic acid has amino and acid groups whereby it reads on the broader recitation of amino acid.

Claim 1 has been amended to recited "at least one organic amine selected from the group consisting of "arginine, histidine, aspartic acid, glutamic acid, serine, threonine, cysteine, phenylalanine, isoleucine, monoethanolamine, diethanolamine, triethanolamine, trometamol, 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid, 1,4-bis(2-sulfoethyl)-piperazine, ethylene diamine, trimethylene diamine, N,N'-bis(3- sulfopropyl)ethylene diamine, aminomethylsulfonic acid and aminoethylsulfonic acid". Accordingly, claim 1 recites organic amines, some of which are amino acids.

Claim 5 is amended to recite "wherein the organic amine is an amino acid selected from the group consisting of arginine, histidine, aspartic acid, glutamic acid, serine, threonine,

cysteine, phenylalanine and isoleucine". Accordingly, claim 5 further defines the organic amine to be an amino acid, and recites specific amino acids.

In view of the amendments to claims 1 and 5, reconsideration and withdrawal of the rejection are respectfully requested.

II. Characteristics of the Present Invention

The method for treating inflammatory diseases of amended claim 1 recites the following features:

(I) administering to the eye an aqueous eye drop comprising

(1) 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof and

(2) at least one organic amine selected from the group consisting of arginine, histidine, aspartic acid, glutamic acid, serine, threonine, cysteine, phenylalanine, isoleucine, monoethanolamine, diethanolamine, triethanolamine, trometamol, 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid, 1,4-bis(2-sulfoethyl)-piperazine, ethylene diamine, trimethylene diamine, N,N'-bis(3-sulfopropyl)ethylene diamine, aminomethylsulfonic acid and aminoethylsulfonic acid,

(3) once a day, and

(II) maintaining a therapeutically effective concentration of 2-amino-3-(4-bromobenzoyl)phenylacetic acid in the anterior aqueous humor of the eye.

The aqueous eye drop used in the method of claim 1 shows the excellent effect of maintaining a therapeutically effective concentration of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or salt or hydrate thereof (hereinafter "bromfenac") in the anterior aqueous humor of the eye, and it treats inflammatory diseases of eye. Intraocular penetration of bromfenac is caused by the interaction between bromfenac and the specific organic amines defined in claim 1.

Experimental Examples 1 and 2 in the specification demonstrate the superior and unexpected effects of the claimed method (see page 20, line 2 to page 26, line 2). For example, Table 3 on page 23 shows that formulations 2 and 3 unexpectedly maintain a therapeutically effective concentration of bromfenac as compared to formulation 1, which does not include an organic amine (see page 22, line 9 – page 23, line 7). These are superior and unexpected results.

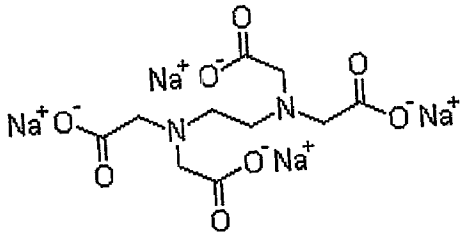
III. Claim Rejection Under 35 U.S.C. § 102

The Examiner rejects claims 1 and 3 under 35 U.S.C. § 102(b) as being anticipated by Ogawa et al. (US 4,910,225). As applied to the amended claims, Applicants respectfully traverse the rejection.

Ogawa et al. describe an ophthalmic composition for inflammatory eye disease, which comprises a sodium salt of bromfenac. However, Ogawa et al. do not disclose an organic amine selected from the group consisting of arginine, histidine, aspartic acid, glutamic acid, serine, threonine, cysteine, phenylalanine, isoleucine, monoethanolamine, diethanolamine, triethanolamine, trometamol, 2-4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid, 1,4-bis(2-sulfoethyl)-piperazine, ethylene diamine, trimethylene diamine, N,N'-bis(3-sulfopropyl)ethylene diamine, aminomethylsulfonic acid and aminoethylsulfonic acid, as recited in claim 1.

The organic amine is a fundamental ingredient in the aqueous eye drop of the claimed method.

Sodium edetate (EDTA), as indicated by the Examiner, is an organic amine, and is represented by the formula:



It is clear from the above-formula that EDTA is quite different in structure from the organic amines recited in claim 1.

Therefore, Ogawa et al. do not disclose the method of claim 1. Accordingly, the reference does not disclose the method for treating inflammatory diseases, having the combination of features of (I)-(1), (I)-(2), (I)-(3) and (II), as mentioned above.

Accordingly, claim 1 is not anticipated by Ogawa et al.

Claim 3 depends from claim 1, and thus also is not anticipated by the reference.

IV. Claim Rejections Under 35 U.S.C. § 103

A. Ogawa et al. in view of Kessler

The Examiner rejects claims 5 and 9-10 under 35 U.S.C. § 103(a) as being unpatentable over Ogawa et al., as applied to claims 1 and 3, in view of Kessler (US 5,849,291). As applied to the amended claims, Applicants respectfully traverse the rejection.

As discussed above, Ogawa et al. do not disclose the organic amine recited in the method of claim 1. The reference discloses EDTA as an inactive ingredient of the ophthalmic solution, and a sodium salt of bromfenac. However, EDTA is structurally different from all of the organic amines recited in claim 1.

Moreover, Ogawa et al. do not teach or suggest that EDTA is equivalent to, or replaced with one of the organic amines recited in claim 1.

Further, the reference does not teach or suggest the specific combination of features (I)-(l), (I)-(2), (I)-(3) and (II) identified above.

Kessler does not remedy these deficiencies. The reference describes an ophthalmic non-irritating iodine anti-infective medicament liquid for treating the eye. As the buffer agent to be added in the medicament liquid, the reference mentions glycine, phthalate acid, citric acid, and PIPES (piperaine-N,N'-bis[2-ethanesufonic acid] and 1,4-piperazinediethanesulfonic acid) (see column 7, lines 3-16 and claim 4). However, these buffer agents are different from the organic amine recited in claim 1.

These buffer agents are also different from the water-soluble polymer and sulfite used to adjust the pH described on column 3, lines 12-15 of Ogawa et al.

Further, Kessler does not teach or discuss bromfenac or a salt or hydrate thereof.

Accordingly, a person skilled in the art would not have combined Ogawa et al. with Kessler.

Moreover, even if one had combined Ogawa et al. with Kessler, one would not have arrived at the presently claimed method having features (I)-(1) and (I)-(2).

Experimental Example 1 of the present specification shows that boric acid exerts the buffering activity of pH 7.8, and it could not increase penetration of bromfenac into aqueous humor (see pages 20-23).

The effect of increasing the penetration of bromfenac into aqueous humor is not common with buffering agents. It can only be attained only by applying the organic amine as defined in claim 1. Thus, there would have been no reason or rationale to combine Ogawa et al. with

Kessler.

For the foregoing reasons, claim 1 would not have been obvious over Ogawa et al. in view of Kessler.

Claims 3, 5, 9 and 10 depend from claim 1, and thus also would not have been obvious over the references.

B. Ogawa et al. in view of Kato et al.

The Examiner rejects claims 5 and 10-11 under 35 U.S.C. § 103(a) as being unpatentable over Ogawa et al., as applied to claims 1 and 3 above, in view of Kato et al. (US 5,945,121). As applied to the amended claims, Applicants respectfully traverse the rejection.

As discussed above, Ogawa et al. do not teach or suggest the organic amines recited in the method of claim 1. The Examiner admits that the reference does not disclose taurine (aminosulfonic acid).

Nevertheless, the Examiner asserts that it would have been obvious to incorporate taurine into a composition for treating an inflammatory condition, such as dry eye, because it is obvious to combine two compositions, each of which is allegedly useful for the same purpose in order to form a third composition that is used for the same purpose (see Office Action, page 7, second full paragraph).

The Supreme Court, in *KSR v. Teleflex*, identified a number of rationales to support a conclusion of obviousness. The Examiner appears to be relying on rationale (A): combining prior are elements according to known methods to yield predictable results (see MPEP 2143). To reject a claim based on this rationale, the Examiner must articulate the following:

(1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;

(2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately;

(3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness (see MPEP 2143).

Kato et al. describe what the liposome eye drops comprising taurine, glucose and inorganic salts, which are useful for treating dry eye or **mitigating dry eye symptoms**. Thus, taurine is used as an active ingredient in the reference for treating dry eye or mitigating its symptons.

On the other hand, Ogawa et al. is directed to a local administration therapeutic composition for **inflammatory disease**, which comprises bromfenac as an active ingredient (see column 1, lines 7-10 and column 2, lines 47-59). Ogawa et al. disclose additional buffer solutions, and anti-inflammatory agents and chelating agents, such as EDTA (see column 3, line 43 – column 4, line 34). However, the reference provides no reason or rationale to include an organic amine, such as taurine in the dry eye composition.

In the method of claim 1, a sodium salt of bromfenac is an active ingredient, and taurine is used to maintain a therapeutically effective concentration of bromfenac in the interior aqueous humor to treat inflammatory diseases of the eye. It is not used as an active ingredient.

Each of the ingredients in Kato et al. and Ogawa et al. show different actions and affects. Thus, a person of ordinary skill in the art would recognize that each of these elements performs a different function in the composition of each reference. Therefore, the Examiner has not made a finding that one of ordinary skill in the art could have combined the elements recited in claim 1 by known methods, and that **each element would perform the same function as it does separately**.

Further, the Examiner has not properly made a finding that one of ordinary skill in the art would have recognized that **the results of the combination were predictable**.

Accordingly, a *prime facie* case of obviousness has not been made. Therefore, the method of claim 1 would not have been obvious over the references.

Claims 5 and 10-11 depend from claim 1, and thus also would not have been obvious over the reference.

Moreover, Applicants wish to point out that where a quaternary ammonium salt, such as benzalkonium chloride, is added to a combination solution comprising bromfenac sodium and tobramycin, precipitation and suspensions formation occurs (see paragraphs [0065] and [0071] of US 2007/0082857, copy enclosed).

The precipitation and suspensions formation can be avoided by adding a water soluble polymer and sulfite, and adjusting the pH to about 6-9 (see column 3, lines 7-15 of Ogawa et al.). However, in the method of claim 1, the combination of bromfenac with an organic amine, unexpectedly increases intraocular penetration.

A person of ordinary skill in the art would not expect an organic amine, such as taurine or trometamol, to act favorably to an aqueous bromfenac solution because an organic amine, such as benzalkonium chloride, acts unfavorably to an aqueous solution of bromfenac, as taught by Ogawa et al.

C. Miyagi et al. in view of Ogawa (2)

The Examiner rejects claims 1, 3, 5-7 and 9-10 under 35 U.S.C. § 103(a) as being unpatentable over Miyagi et al. (US 6,281,224) in view of Ogawa et al. (Effects of bromfenac sodium, non-steroidal anti-inflammatory drug, on acute ocular inflammation) ("Ogawa (2)"). As applied to the amended claims, Applicants respectfully traverse the rejection.

Miyagi et al. describes a pranoprofen ophthalmic solution containing an organic amine.

The method of claim 1 recites "administering to the eye an aqueous eye drop comprising [bromfenac] or its pharmacologically acceptable salt or a hydrate thereof". The Examiner admits that Miyagi et al. do not disclose bromfenac, but asserts that it would have been obvious to substitute pranoprofen for bromfenac for the treatment of ocular inflammation because bromfenac would be more effective that pranoprofen (see Office Action, page 8, last paragraph). Applicants respectfully disagree.

The properties of pranoprofen are quite different from those of bromfenac. For example, a comparison of the distribution of pranoprofen and bromfenac after the administration to the eyes is shown below.

Table 1

Bromfenac	Radioactivity concentration (ng eq. of bromfenac sodium/g or ml)	
	30 min	(ratio)
Cornea	1690.4± 155.2	(2.069)
Conjunctiva	817.1± 174.0	(1.000)
Aqueous humor	95.4 ± 29.0	(0.423)
Iris & ciliary body	225.4 ± 23.9	(1.000)

This data is described on page 35, Table 1 of Yakubutsu Doutai, 14(1): 3 2-41 (1999), a copy of which is enclosed. An English language abstract of the reference is also enclosed.

Table 2

Pranoprofen	Radioactivity concentration (ng/ml tissue)	
	30 min	(ratio)
Cornea	18	(1.385)
Conjunctiva	13	(1.000)
Aqueous humor	10	(1.25)
Iris & ciliary body	8	(1.00)

This data is disclosed in the two graphs on the left of page 20 of Interview Form of Medicines, April of 2006, NIFLAN OPHTHALMIC SOLUTION, Eye Drops of Pranoprofen. A copy of the reference and an English translation of the two graphs are enclosed.
Dose of pranoprofen: 0.04 mg/40μL/eye
The dose was calculated from the description on page 20, lines 13-14 which is underlined. The English translation of the underlined portion is: "A 0.1 % ^{14}C-pranoprofen ophthalmic solution was administered to both eyes of rabbits at a dose of 0.01 ml/once, in total four times every 3 minutes".

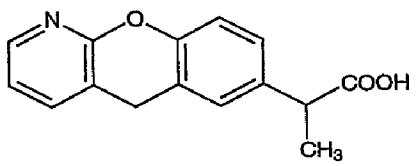
As is clear from Tables 1 and 2, showing the concentration in the extraocular tissue at 30 min. after administration, the ratio of the concentration in the cornea to the concentration in the conjunctiva is quite different between bromfenac and pranoprofen. With regard to bromfenac, the ratio of the concentration in the cornea/concentration in the conjunctiva is 2.069. On the other hand, with regard to pranoprofen, the ratio of the concentration in cornea/the concentration in the conjunctiva is 1.385.

Further, as is clear from Tables 1 and 2, showing the concentration in the intraocular tissue at 30 min. after administration, the ratio of the concentration in the aqueous humor to the concentration in the iris and ciliary body is quite different between bromfenac and pranoprofen. With regard to bromfenac, the ratio of the concentration in the aqueous humor/the concentration in the iris and ciliary body is 0.423. On the other hand, with regard to pranoprofen, the ratio of the concentration in the aqueous humor/the concentration in the iris and ciliary body is 1.25.

Even though Miyagi et al. describe on column 2, lines 60-63 that they studied the stability of an eye drop by adding an organic amine to pranoprofen, there is no teaching or suggestion to replace pranoprofen with bromfenac. As discussed above, they have very different intraocular penetration properties.

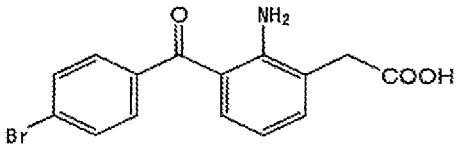
Furthermore, pranoprofen is structurally different from bromfenac, as shown below.

Pranoprofen



α-methyl-5H-[1]benzopyrano[2,3-b]pyridine-7-acetic acid, (see The Merck Index 2001, 13th Edition, page 1377, item 7796).

Bromfenac



Thus, pranoprofen is a condensed tricyclic-propionic acid derivative, and bromfenac is a substituted phenyl-acetic acid derivative.

Further, the physico-chemical properties of pranoprofen and bromfenac are much different.

For example, the pharmacological effect of bromfenac is 10 times greater than pranoprofen, as is clear from the disclosure on page 406, right column, lines 2-5 of the English

language abstract of "Effects of Bromfenac Sodium, Non-steroidal Anti-inflammatory Drug, on Acute Ocular Inflammation", Nippon Ganka Gakkai Zasshi, 1995, vol. 99 no. 4, pages 406-411 (the full Ogawa (2) reference) (copy enclosed).

Further, Miyagi et al. describe on column 2, lines 60-63, that stability of an eye drop is enhanced by adding an organic amine to pranoprofen.

Thus, Miyagi et al. and Ogawa (2) do not teach or suggest the effect of retaining a therapeutically effective concentration of a drug at a target region of the eye by administration once a day, based on the effect of promoting intraocular penetration of the drug.

Therefore, it would not have been obvious to a person skilled in the art to substitute bromfenac for pranoprofen in the composition of Miyagi et al.

Moreover, even if the Miyagi et al. reference were combined with Ogawa (2), the effect of retaining a therapeutically effective concentration of a drug at the target region of the eye by administration once a day, based on the effect of promoting intraocular penetration of drug, would not have been obvious to one of ordinary skill in the art.

Therefore, claim 1 would not have been obvious over the references.

Claims 3, 5-7 and 9-10 depend directly from claim 1, and thus also would not have been obvious over the references.

Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

V. Conclusion

For these reasons, Applicants take the position that the presently claimed invention is clearly patentable over the applied references.

Therefore, in view of the foregoing amendments and remarks, it is submitted that the rejections set forth by the Examiner have been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

Shirou SAWA et al.

By /Andrew B. Freistein/

Digitally signed by /Andrew B. Freistein/
DN: cn=/Andrew B. Freistein/, o=WLP, ou=WLP, email=afreistein@wenderoth.com, c=US
Date: 2010.02.05 14:26:18 -05'00'

Andrew B. Freistein
Registration No. 52,917
Attorney for Applicants

ABF/emj
Washington, D.C. 20005-1503
Telephone (202) 721-8200
Facsimile (202) 721-8250
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